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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAYES, ROBERT CLINTON	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,512	AOKI ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *28 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date ___.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The amendment filed 9/28/04 has been entered.

2. The oath or declaration remains defective, as previously made of record, because no information is provided within the box for identifying the mailing address (P.O.Box) of each inventor. Note that residence is not the same as the P.O.Box unless indicated as such in the oath. Again, the mailing address may be provided in an application data sheet or a supplemental oath or declaration. Note that resubmission of the originally submitted oath does not address this objection, and that no application data sheet was provided with the required P.O. Boxes on either 4/30/01 or with the instant response, in contrast to Applicants' assertions on page 6 of the response. See 37 CFR 1.63(c) and 37 CFR 1.76.

3. The rejection of claim 13 under 35 U.S.C. 112, first paragraph, for new matter is withdrawn due to the cancellation of this claim.

4. The rejection of claims 11 & 13 under 35 U.S.C. 112, second paragraph, for the recitation of a "*substantially* reduced response" is withdrawn due to the cancellation of these claims.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Applicants' arguments filed 9/28/04 have been fully considered but they are not deemed to be persuasive.

7. New claims 19 & 24 are rejected on the grounds of *res judicata* (MPEP 706.03 (w)), as the issues presented by these claims are the same as those decided by the Board of Appeals and Interferences in a decision dated November 28, 2000 (*Ex parte* Aoki et al., Appeal No. 1997-2367). In contrast to Applicants' assertions, merely including a long Markush group of disorders to be treated (which the references from the upheld rejection under 35 U.S.C. 103 also teach) versus treating any generic "neuromuscular condition" does not change the issue previously decided by the Board. In other words, listing nearly all known "neuromuscular disorders or conditions" now in a Markush group does is not patently distinct from that previously decided by the Board, in which the same patient population "suffering from a neuromuscular disorder or condition" is being treated in both the instant application and in *Ex parte* Aoki et al., Appeal No. 1997-2367. For example, claim 24 still requires administering botulinum toxin type E "after the patient exhibits a loss of clinical responsiveness", which includes the limitation of "after the patient exhibits... neutralizing antibodies to botulinum toxin A", which has already been decided by the Board. See MPEP 706.03(w).

8. Claims 14-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

No proper antecedent basis nor conception in context with that described within the specification at the time of filing Applicants' invention exists for the broader recitation of "the immune response being selected from the group consisting of an allergic response, a delayed-type of hypersensitivity, a serum sickness-like response, and combinations thereof" in both base claims 14 & 24. In contrast, page 4 of the specification alternatively and specifically contemplates an

> "(1) Allergic reaction *where there is immediate local swelling, redness and itching.* This may also be associated with general flu-like symptoms. (2) A delayed-type hypersensitivity *manifested as swelling and redness at the injection site 48 to 72 hours after injection.*
> (3) or, a serum sickness-like response *where the patient experiences flu-like symptoms.* [emphasis added]"

where specific symptoms are required to be treated (versus any undescribed/ non-contemplated generic symptoms), where no conception of "combinations thereof" are further contemplated, and where "a loss of clinical responsiveness to botulinum toxin [type A] injections" alternatively must occur first (i.e., before the various immuno-related explanations described within the specification for why this "loss of clinical responsiveness to botulinum toxin" occurred, given a fair reading of the specification (e.g., see the beginning of the second paragraph on page 4); thereby, constituting new matter.

No proper antecedent basis nor conception in context with that described within the specification at the time of filing Applicants' invention exists for the recitation of "the amount of botulinum toxin type E administered to the patient is less than about 300 units" (i.e., as it relates to claim 23). In contrast, page 14 of the specification contemplates administration of "up to

about 300 units, or more", which is different in scope and conception from "less than about 300 units"; thereby, constituting new matter.

No proper antecedent basis nor conception in context with that described within the specification at the time of filing Applicants' invention exists for the recitation of "treat a neuromuscular disorder or condition selected from… Parkinson's…". In contrast, page 5 of the specification contemplates treating "Parkinson's *and limb (focal)* ***dystonia***" , which is entirely different in scope than treating Parkinson's disease itself (i.e., as it relates to claims 19-24); thereby, constituting new matter.

9. Claims 14-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using botulinum toxins to treat muscle spasms/dystonia, does not reasonably provide enablement for administrating botulinum toxins to generically treat patients following "an allergic reaction, a delayed-type hypersensitivity, or a serum sickness-*like* response", or for treating neurological disease states. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to know how to use the invention commensurate in scope with these claims.

The specification describes treating muscle spasms/dystonia with botulinum toxin A, and then treating such disorders with botulinum toxin E after "clinical responsiveness" to botulinum A ceases. Although various possible explanations as to why botulinum toxin A ceases to work are listed (e.g., see page 4 of the specification), it is not reasonable to extrapolate from the limited guidance provided within the specification to now generically treat neurological disorders such as Parkinson's disease, spina bifida, animus (i.e., "ill will or hostility"), or tension

headaches (especially after the "patient exhibits [any generic] immune response... [such as] an allergic condition, a delayed-type of hypersensitivity, a serum sickness-*like* response, and combinations thereof"), which are not caused by muscle spasms/dystonia. For example, allergic responses caused by administration of botulinum toxin A would reasonably imply to the skilled artisan that the patient is most likely allergic to such injections, and such treatment should stop immediately to prevent anaphylactic shock (i.e., also a hypersensitivity) and possibly death. In other words, the specification's lack of guidance as to what metes and bounds "an allergic condition, a delayed-type of hypersensitivity, and a serum sickness-*like* response" entail, as now recited in the claims, and how these putative responses are related to knowing when to treat different neuromuscular disorders would prevent the skilled artisan from knowing how to treat such conditions, as currently claimed (i.e., as it relates to claims 14-18 & 24). Likewise, injecting botulinum toxin into the brain (i.e., for putatively treating Parkinson's disease or tension headaches or "ill will or hostility") is not a reasonable treatment for these disorders because it may interfere with the basal forebrain cholinergic neurons present within the brain, and possibly lead to temporary Alzheimer-like symptoms (i.e., because Alzheimer's disease is characterized by a loss of this specific population of neurons). Similarly, direct injection of botulinum toxins into the spina cord to putatively treat "spina bifida" is not reasonable because interfering with cholinergic transmission here may lead to ALS-like symptoms (e.g., by interfering with motor neuron transmission) and/or potentially turn off the cholinergic component of the autonomic nervous system (e.g., heart or lung function, etc.); thereby, leading directly to death (i.e., as it relates to claims 19-24). In other words, the skilled artisan would not know how to use the invention, as now broadly and generically claimed, without requiring undue

experimentation to keep the patient alive long enough to determine whether the invention worked, and because these disorders are not caused by uncontrolled cholinergic neuron transmission amenable to botulinum administration. It is suggested that the claims be amended to reflect the invention actually described within the specification (i.e., treating muscle spasms/dystonia following loss of clinical responsiveness to the administration of botulinum toxin type A...) to obviate this rejection.

10. Claims 15-18 & 20-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear what the recitation "less than about" or "at least about" exactly entails. For example, "about" reasonably refers to a range around 300 units $\pm$ 5%. The recitation "less than" or "at least" removes the upper or lower limit, respectively, of the claimed range of about 300 units; thereby being contradictory and ambiguous.

11. Claims 19-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is confusing and makes little sense how "animus" (i.e., "ill will or hostility") or "spina bifia" or "tension headaches" are considered "neuromuscular disorders", which are putatively amenable to treatment with botulinum toxins.

12. Claims 19-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ludlow et al. (IDS Ref #ac), in view of Simpson et al. (IDS Ref #ag) and Janovic et al. (IDS Ref #ae), for the reasons made of record for cancelled claims 11-13 in Paper No: 20040624, and as follows.

Applicants argue on pages 9-13 of the response that "the combination of Ludlow, Simpson, and Jankovic does not disclose, teach, or suggest the present invention", and relies on submitted papers that teach that cross-reactivity of antibodies is possible, under some circumstances, and therefore, such cross-reactivity would "block the therapeutic effectiveness of type E". In contrast to Applicants' assertions, all the references relied upon in the pending rejection under 35 U.S.C. 103 (i.e., Ludlow et al, Simpson et al, and especially Jankovic et al) teach that "[i]t is likely that patients with antibodies against botulinum toxin will respond to injections with other botulinum toxins that are immunologically distinct from type A" (page 1189, column 1, Jankovic). Therefore, arguments consistent with Applicants' invention itself not being enabled, because "antibodies to type A may cross-react with type E and block the therapeutic effectiveness of type E", are not consistent with that expected within the art at the time of filing Applicants' invention, as evidenced by the teachings of Ludlow et al, Simpson et al, and Jankovic et al, which alternatively provide motivation for the instant rejection, as discussed above. Therefore, Applicants' arguments are not persuasive, because they are not on point, and contradict the workability of Applicants' own invention. Accordingly, the Board in *Ex parte* Aoki et al., Appeal No. 1997-2367) itself stated that:

> "We would remind appellants that absolute predictability is not required. For obviousness under 103, all that is required is a reasonable expectation of success. In re O'Farrell, 853 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)."

In summary, Ludlow et al teach the treatment of neuromuscular disorders such as torticollis and oromandibular dystonia (movement disorders characterized by muscle spasm/spasmodic activity) by intramuscular injection of botulinum toxin type F after the patients had already been treated with botulinum toxin type A (i.e., with 1/4 of the dose of type A; pg. 350, 1st full *pp*) and had developed neutralizing antibodies to the type A toxin (i.e., as manifested as a reduced response to type A toxin; pages 349-350; as it relates to claims 19 & 24). In particular, Ludlow teach dosages of "at least about 300" in Table 1 for the second botulinum (type F) injection (e.g., patient 1: 285 (i.e., about 300 $\pm$ 5%) twice + 150 = 720; as it relates to claim 22). Ludlow also teach treatment of patients with "less than 300 units" of the second botulinum toxin (e.g. 40 units; Table 1; as it relates to claim 23), which means that 160 units of botulinum toxin type A was previously administered (i.e., as it relates to being "less than about 1000/500 units" of type A, as it relates to claims 20-21; and "from about 80 units to about 460 units" of type A, as it relates to claim 23). However, Ludlow et al do not teach administration of botulinum toxin type E after administration of botulinum toxin type A.

Simpson et al teach that all of the botulinum serotypes A, B, C1, C2, D, E, F and G are produced by the same species of bacterium, and provide a review of their pharmaceutical activities. In particular, all of the botulinum serotypes block acetylcholine release for nerve endings, and each of the serotypes are taught to be "antigenically distinct" (e.g., pages 155-156). Therefore, it is reasonable to expect that administration of any of the serotypes would produce the same physiological effect of blocking cholinergic neuronal transmission by "interrupt[ing] transmission at the muscle end organ" (i.e., reduced muscle spasm/twitch; pages 163-164 &

167). Accordingly, because the serotypes differ antigenically, antibodies developed against a first administered serotype would not be expected to block the activity of a second serotype at the cholinergic receptor. This is consistent with the teachings of Ludlow et al, who teach that the advantage of administering a second serotype toxin is to overcome the reduced responsiveness to the first toxin.

Further, consistent with both the teachings of Ludlow et al and Simpson et al, Jankovic et al teach that botulinum toxin is used for the treatment of neuromuscular disorders such as muscle spasm/back spasms, strabismus, comitant and vertical strabismus, lateral rectus palsy, nystagmus, dysthyroid myopathy, writer's cramp, blepharospasm (page 1187, first column); Wilson's disease, tardive dystonia, laryngeal dystonia, tardive dyskinesia, Parkinson's and limb/foot focal dystonia, tremor (pages 1187, second column & 1190, second column; Table 1); tics, segmental myoclonus, spasms due to chronic multiple sclerosis, spasms due to abnormal bladder control in patients with spinal cord injury, anismus (page 1191, second column; as it relates to claim 19). Jankovic et al also teach that "blocking"/neutralizing antibodies develop to the toxin (i.e., an immune response), which cause patients to be nonresponsive to the toxin (page 1189, column 1; as it relates to claim 24). Jankovic et al then conclude that "[i]t is likely that patients with antibodies against botulinum toxin will respond to injections with other botulinum toxins that are immunologically distinct from type A" (page 1189, column 1).

Thus, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to use Ludlow's methods of administering botulinum toxin type A to treat movement disorders characterized by muscle spasm/dystonia, followed by administration of another botulinum toxin, such as type E as taught by Simpson or Jankovic, in order to continue

reducing muscle spasms/dystonia in these patients. It is emphasized that both Simpson et al and Jankovic specifically suggest administration another botulinum serotype toxin after patients become nonresponsive to a first botulinum toxin (i.e., type A). In that Ludlow teach that a reduced response to type A toxin probably is due to development of neutralizing antibodies to the type A toxin, administration after a "loss of clinical responsiveness" in clinical symptoms would be obvious, in order to maintain a positive clinical response for the patient.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday, and alternate Fridays, from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on (571) 272-0961. The fax phone number for this Group is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert C. Hayes, Ph.D.
December 8, 2004

ROBERT C. HAYES, PH.D.
PATENT EXAMINER